REMARKS

Claims 1-138 pending in this application and are subject to restriction to eleven groups:

Group I, claims 26-31 and 59-61, alleged by the Office to be directed to a recombinant myeloma cell comprising a polynucleotide sequence encoding a dominant negative mismatch repair protein and a recombinant, hypermutable mammalian expression cell comprising a dominant negative mismatch repair gene;

Group II, claims 32-40 and 49-58, alleged by the Office to be directed to a method for producing mammalian expression cells that produce high titers of antibody from *in vitro* immunized immunoglobulin producing cells comprising cloning immunoglobulin genes from a hybridoma into a mammalian expression cell wherein said expression cells express a dominant negative allele of a mismatch repair gene;

Group III, claims 41-48, alleged by the Office to be directed to a method for producing mammalian expression cells that produce high titer high affinity antibody comprising cloning immunoglobulin genes from hybridoma cells expressing a dominant negative allele of a mismatch repair gene into a mammalian expression cell;

Group IV, claims 62-80, 135, and 136, alleged by the Office to be drawn to a method for producing hybridoma cells that produce high affinity antibodies from *in vitro* immunized immunoglobulin producing cells and a method for producing hybridoma cells that produce high affinity antibodies from *in vitro* immunized immunoglobulin producing cells, both methods comprising incubating parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma cells;

Group V, claims 81-90, 135, and 136, alleged by the Office to be drawn to a method for producing mammalian expression cells that produce high affinity antibodies from *in vitro* immunized immunoglobulin producing

cells comprising cloning immunoglobulin genes from hybridomas into mammalian expression cells and incubating said expression cells in the presence of at least one chemical inhibitor of mismatch repair;

Group VI, claims 91-101, 135, and 136, alleged by the Office to be directed to a method for producing mammalian expression cells that produce high titers of high affinity antibodies to a selected antigen from *in vitro* immunized immunoglobulin producing cells comprising incubating hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair to form hypermutated hybridoma cells and cloning immunoglobulin genes from said hypermutated hybridoma cells into a mammalian expression cell;

Group VII, claims 102-106, alleged by the Office to be drawn to a method for producing high affinity antibodies from *in vitro* immunized immunoglobulin producing cells in high titers comprising combining donor cells comprising immunoglobulin producing cells with an immunogenic antigen *in vitro* wherein said donor cells are naturally deficient in mismatch repair;

Group VIII, claims 107-113, alleged by the Office to be directed to a method for producing hybridoma cells that produce high affinity antibodies from *in vitro* immunized immunoglobulin producing cells in high titers comprising combining immunoglobulin producing cells with an immunogenic antigen *in vitro* and fuding said immunoglobulin producing cells with myeloma cells which are naturally deficient in mismatch repair;

Group IX, claims 114-123, 135, and 136, alleged by the Office to be directed to a method for producing mammalian expression cells that produce high affinity antibody in high titers from *in vitro* immunized immunoglobulin producing cells comprising combining donor immunoglobulin producing cells which are naturally deficient in mismatch repair with myeloma cells and cloning immunoglobulin genes from the resulting hypermutated hybridoma into a mammalian expression cell;

Group X, claims 124-133, 135, and 136, alleged bythe Office to be drawn to a method for producing mammalian expression cells that produce high affinity antibody in high titers from *in vitro* immunized immunoglobulin producing cells comprising combining donor immunoglobulin producing cells with myeloma cells which are naturally deficient in mismatch repair and cloning immunoglobulin genes from the resulting hypermutated hybridoma into a mammalian expression cell; and

Group XI, claim 134, alleged by the Office to be directed to a method for *in vitro* production of antigen-specific immunoglobulin producing cells comprising isolating donr cells from an animal, treating said cells with L-leucyl-leucine methyl ester, incubating said donor cells with an immunogenic antigen *in vitro* at 25-37 degrees in a medium supplemented with 5-15% serum and a growth promoting cytokine for 4 days, followed by washing of the cells in medium and further culturing in a medium supplemented with 5-15% serum for an additional 8 days, thereby stimulating the production an antigen-specific immunoglobulin producing cells.

Applicants respectfully traverse the restriction requirement because a search and examination of the subject matter recited in the pending claims of at least Groups IV, V, and VI can be conducted without a serious burden as explained below. Nevertheless, in accordance with 37 CFR § 1.143, Applicants hereby provisionally elect the subject matter of Group IV for prosecution on the merits.

The purpose of 35 U.S.C. § 121 is to avoid the necessity of conducting separate and diverse searches of claims directed to independent or distinct subject matter. Separate and diverse searches would not be required for Groups IV, V, and VI of the present application, however, because the relationship among the claimed subject matter is such that a search of the subject matter encompassed by the claims of Group IV would necessarily lead to disclosures, to the extent that any exist, of the subject matter encompassed by the claims of Group V and Group VI. For example, a comprehensive search of methods for producing hybridoma cells that produce high affinity antibodies from *in vitro* immunized immunoglobulin producing cells by incubating parental hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair, thereby forming hypermutated hybridoma

cells, the subject matter, *inter alia*, of Group IV, would necessarily lead to specific disclosures, to the extent that any exist, of methods for producing mammalian expression cells that produce high affinity antibodies from *in vitro* immunized immunoglobulin producing cells by cloning immunoglobulin genes from hybridomas into mammalian expression cells and incubating said expression cells in the presence of at least one chemical inhibitor of mismatch repair, the subject matter of Group V, as well as methods for producing mammalian expression cells that produce high titers of high affinity antibodies to a selected antigen from *in vitro* immunized immunoglobulin producing cells by incubating hybridoma cells in the presence of at least one chemical inhibitor of mismatch repair to form hypermutated hybridoma cells and cloning immunoglobulin genes from said hypermutated hybridoma cells into a mammalian expression cell, the subject matter encompassed by Group VI. Accordingly, a search and examination of the subject matter encompassed by Groups IV, V, and VI would not impose a serious burden on the Examiner. Applicants respectfully request reconsideration and withdrawal of the restriction requirement with respect to those Groups.

Conclusion

Applicants believe that the foregoing constitutes a complete and full response to the Office Action of record. Accordingly, an early and favorable Action is respectfully requested.

Respectfully submitted,

Date: March 21, 2007

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